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EVIDENCE OF GENETIC INSTABILITIES AMONG HYPOTHYROID WOMEN WITH BOH

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ABSTRACT

Hypothyroidism is one of the most common endocrine disorders in women of reproductive age. Bad obstetric history (BOH) is the common complication of pregnancy, affecting approximately 15% of all clinically recognized pregnancies. Hypothyroidism in women during pregnancy leads to bad obstetric complications like two or more consecutive miscarriage, placental abruption and fetal death. Thus, the present study was undertaken to detect the biochemical & cytogenetic aspects on hypothyroid women with bad obstetric history. The objectives of the present studies are to evaluate the extent of DNA damage and chromosome abnormalities in hypothyroid women experiencing BOH and to assess various demographic, physiological and lifestyle characteristics of hypothyroid women suffering from BOH. The CBMN assay revealed that a statistically significant increase in the mean CBMN frequency among hypothyroid women experiencing BOH. Moreover, there is an association between the extent of DNA damage and various lifestyle and physiological risk factors. The present study proved an increased extent of somatic DNA damages among hypothyroid women experiencing BOH. So maternal hypothyroidism in early gestation is severely affecting the fetal brain development and also has an association between pregnancy complications.

INTRODUCTION

Thyroid dysfunction and/or antibodies are relatively common during gestation (Allan WC et al, 2000; Casey BM et al, 2005), and they have been thought to represent a risk to maternal and fetal health during pregnancy, although the results from different studies are controversial. Up to now, thyroid dysfunction and/or antibodies have been thought to be associated with pregnancy complications such as placental abruption (Casey BM et al, 2005), gestational diabetes (Cleary-Goldman J et al, 2008; Wikner BN et al, 2008), pregnancy-induced hypertension (Lejeune B et al, 1993), and preeclampsia (Wikner BN et al, 2008; Lejeune B et al, 1993), but these relationships have not been proved.

Bad obstetric history (BOH) is the common complication of pregnancy, affecting approximately 15% of all clinically recognized pregnancies in the general population. BOH also referred as recurrent pregnancy loss (RPL) or Recurrent miscarriages (RM) or Habitual abortion, because these are historically defined as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period. Incidence of BOH was found to be 5.27%, including (1.4%) with history of unexplained stillbirth or neonatal loss. The causes of BOH may be genetic, hormonal, abnormal maternal immune response, maternal infection and anatomical (Nickerson et al., 2012).

Hypothyroidism is one of the most common endocrine disorders in women of reproductive age. The prevalence of overt hypothyroidism during pregnancy has estimated to be 0.3-0.5 % and in addition, 2-3% of pregnant women may suffer subclinical hypothyroidism. The adverse effects of maternal hypothyroidism include a higher risk of perinatal mortality, increased risk of fetal death, increased frequency of low birth weight, hypertension, and impaired mental and somatic development. Today many women are suffering from hypothyroidism during pregnancy that may leads to many obstetric complications. This bad obstetric history is one of the major complications in women that make many problems in the family relationships as well as society. In fact many of them are unaware of the consequences of hypothyroidism during pregnancy. Hence, this study was undertaken to understand the biochemical and cytogenetic factors affecting hypothyroid women with bad obstetric history.

Hypothyroidism is a condition resulting from the under activity of thyroid gland. This leads to the decreased production of thyroid hormones. Maternal hypothyroidism may place the mother at an increased risk of adverse obstetric outcomes. It is known that the fetus is totally dependent on maternal thyroid hormone supply during the 1st trimester of pregnancy which is the crucial time in organogenesis. So hypothyroidism in women during pregnancy leads to bad obstetric complications like two or more consecutive miscarriage, placental abruption and fetal death. Thus the present study was undertaken to detect the biochemical & cytogenetic aspects on hypothyroid women with bad obstetric history. The objectives of the present studies are to evaluate the extent of DNA damage and chromosome abnormalities in hypothyroid women experiencing BOH and to assess various demographic, physiological and lifestyle characteristics of hypothyroid women suffering from BOH.

MATERIALS AND METHODS

55 study subjects suffering from hypothyroidism were taken as study subjects and 20 healthy subjects were selected as control. Detailed demographic, physiological, lifestyle, biochemical and clinical characteristics of subjects were performed using profoma. Cytokinesis Block Micronuclei (CBMN) Assay was performed by using Cytochalasin B for quantitating the extent of somatic DNA damages. Peripheral Blood Lymphocyte Culture (PBLC) was performed to analyze chromosome aberrations. 8ml venous blood was collected

aseptically from all the subjects by venepucture after overnight fasting. 4ml was transferred in to the vacuutainer containing sodium heparin to perform lymphocyte culture and CBMN assay. The remaining 4ml was transferred in to plain tube and allowed to clot. With the serum, sugar and lipid profile were estimated by enzymatic method using semianalyser.

Age, birth order, education, occupation, residence, religion, duration of married life was taken as the demographic characteristics. BMI, no. of spontaneous abortions, no. of gestations, no. of MTPs, history of diabetes, history of thyroid disorders were taken as the physiological parameters. Parental consanguinity, daily water intake were used as the life style characteristics. FBS, total cholesterol, HDL, LDL, triglycerides, level of thyroid hormones, TSH and different clinical conditions are the major parameters used for this study. The distribution of mean CBMN frequency and karyotype according to various parameters of the study subjects were analyzed.

OBSERVATIONS AND RESULTS

The age of the study subjects ranged from 19 to 50 years with a mean age of 34.2 years and age of control subjects ranged from 22 to 49 years with a mean age of 37.15. The birth order ranged from 1 to 9, majority of the study subjects belongs to birth order ranged from 1 to 3. According to number of gestations among 55 study subjects, 52 subjects with 2-5 times of gestation and 3 subjects with 6-9 times of gestations.

The distribution of mean CBMN frequency of the control subjects were 10.93 and study subjects were 13.92. Out of 55 study subjects 5 of them showed abnormal karyotype. The BMI was considered as one of the physiological variable and is categorized in to ≤25 and >25. The high mean CBMN frequency was observed (13.97) in BMI >25 and it showed 3.75% of abnormal karyotype. The BMI ≤25 showed the mean CBMN frequency of 13.87 and showed 11.1% of abnormal karyotype. The incidence of mean CBMN frequency increasing with increased BMI.

Moreover, the increased CBMN frequency was observed among subjects with characteristics like increased birth order, increased body weight, increased duration of married life, history of previous abortions and increased number of gestations and increased number of MTPs. Subjects with increased concentrations of total cholesterol, LDL cholesterol and triglycerides showed a high mean CBMN frequency. Whereas, subjects having low concentrations of HDL cholesterol revealed an increased CBMN frequency. The highest mean CBMN frequency was found to be in subjects with low thyroid hormones and high TSH.

DISCUSSION

Thyroid disorders in early pregnancy may lead to grave consequences, and therefore testing may be appropriate. Hypothyroidism during pregnancy has been clearly associated with adverse pregnancy outcomes such as preeclampsia, gestational hypertension, fetal death, premature delivery, spontaneous abortions, recurrent abortions and cretinism (Abalovich M et al, 2002; Stagnaro-Green A, 2011). The present study was undertaken to evaluate the extent of somatic DNA damages, if any, among hypothyroid women experiencing bad obstetric history.

Thyroid hormones are essential for the growth and metabolism of the growing fetus. Early in pregnancy, the mother supplies her fetus with thyroid hormones. If the mother is hypothyroid, she cannot supply her fetus with enough thyroid hormones. Hence hypothyroidism is a risk factor for pregnancy loss and often linked to recurrent pregnancy loss (Rao V, 2008). Recurrent miscarriage is commonly defined as three or more consecutive pregnancy losses before 20 weeks of amenorrhoea and affects approximately 1% of all couples trying to conceive (Ford HB & Schust DJ, 2009). Predisposing factors include maternal age, parental chromosomal aberrations, uterine abnormalities, antiphospholipid syndrome, immunological and thrombophilic disorders, and endocrine diseases such as hypothyroidism and diabetes mellitus. Unlike sporadic spontaneous miscarriage, recurrent miscarriage more often occurs despite normal fetal cytogenetic findings, and in 50% of cases the underlying cause remains unexplained. There is a known relation between hypothyroidism and recurrent miscarriage (Ford HB and Schust DJ, 2009).

According to Magnus et al (2019), "maternal age and previous miscarriage rates increases the risk of subsequent miscarriages. Women experience an age dependent increase in various adverse reproductive events such as infertility, pregnancy complications". The present study also observed that, increased maternal age is a risk factor for increased mean CBMN frequency and karyotypic abnormalities.

The present study observed that the concentrations of total serum cholesterol, LDL cholesterol and triglycerides were increased consistently with increasing TSH. High levels of triglycerides are often accompanied by low HDL cholesterol, especially in insulin-resistant individuals. A possible mechanism is that HDL particles associated with high triglyceride concentrations may be more readily catabolized. The association between TSH and HDL cholesterol among overweight individuals was substantially attenuated after adjustment for triglyceride level. This may suggest that the negative association between TSH and HDL cholesterol, at least in part, may be mediated by relatively high triglyceride concentrations. Studies of lipid metabolism related to thyroid dysfunction may provide some understanding of mechanisms that could underlie the consistent associations in our study. Thus, high total serum cholesterol and LDL cholesterol may be caused by fewer cell-surface receptors for LDL, resulting in reduced LDL catabolism. For triglycerides, reduced activity of lipoprotein lipase, or impaired clearance of lipoproteins dependent on LDL receptor function, may result in higher levels. However, it should be acknowledged that studies of lipid metabolism related to thyroid dysfunction may not be relevant to explain our findings within the normal range of thyroid function. This shows linear positive associations between TSH in the reference range and concentrations of total serum cholesterol, LDL cholesterol, non-HDL cholesterol and triglycerides, and a linear negative association with HDL cholesterol. The present study also showed similar observations. Increased level of FBS, triglycerides, total cholesterol, LDL cholesterol showed high mean CBMN frequency. Whereas decreased level of HDL showed high mean CBMN frequency. Moreover, the concentration of TSH showed a positive association with total serum cholesterol and LDL cholesterol and a negative association with HDL cholesterol

According to Saki et al (2014), prevalence of hypothyroidism in pregnant woman was 13.7% (clinical- 2.4% and subclinical- 11.3%). Hypothyroidism and subclinical hypothyroidism had a significant association with IUGR. The current study also showed high mean CBMN frequency among BOH women having clinical condition of IUGR.

CONCLUSIONS

From these findings it can be concluded that hypothyroidism is occurs as a multi-factorial influences, among this some of them are modifiable and others are not. The present study proved that hypothyroidism is one of the major causes of bad obstetric complications. So maternal hypothyroidism early in gestation is severely affecting the fetal brain development and also has an association between pregnancy complications.

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